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The effects of Sevoflurane and Propofol on IFN-γ And IL-12 Study On Patients With Craniotomy Surgery

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Abstract— *Background: This research aimed to analyze the effects of sevoflurane and propofol on IFN-γ and IL-12, the study on patients with craniotomy surgery. The treatment is the anesthesia with sevoflurane or propofol for more than 2 hours. The levels of IFN-γ and IL-12 are measured just before induction of anesthesia and just after anesthesia with sevoflurane or propofol is stopped.*

Methods: The study design is an observational study by using pre-and-post design. The subjects are patients aged 30-55 years old who were undergoing craniotomy surgery for tumor removal at Dr. Kariadi Hospital. The differences in the means before and after the same anesthesia agent were analyzed with paired T-test if the data distribution is normal, or with the Wilcoxon rank-sum test if the data distribution is not normal. The difference in the means between the two different anesthesia agents was analyzed using an independent T-test if the data distribution is normal, or with the Mann-Whitney test if the data distribution is not normal.

Results: It was observed that sevoflurane and propofol increased the level of IFN-γ and IL-12 but not significant. There were differences between IFN-γ and IL-12 before and after anesthesia with sevoflurane compared with propofol. Therefore, the hypothesis was accepted. This shows that the originality of this research has been statistically and empirically proved.

Conclusion: The increase of both IFN-γ and IL-12 levels after anesthesia with propofol is significantly higher than those with sevoflurane. Propofol exerts a bigger pro-inflammatory response than sevoflurane in patients undergoing craniotomy surgery.

Keywords— ***Effects Of Sevoflurane, Propofol, IFN-γ, IL-12, Craniotomy Surgery.***

I. INTRODUCTION

The immune system is important to live because there are a lot of hazardous pathogens in the environment. The immune system will protect us from those pathogens and diseases. The immune system identifies and eliminates pathogens by inducing innate immune responses and then adaptive response. Immunity innate, often known as normal or initial immunity, it is the first line of defense and refers to the system of protection that occurs long before infection."The key component of innate immunity is the epithelial membrane that prevents the entry of bacteria, phagocytic cells (neutrophils and macrophages), dendritic cells, natural killer cells (NK), and other plasma proteins, including the complementary network. Innate immunity's critical cellular reaction is inflammation, the mechanism by which phagocytic cells are recruited and stimulated to remove microbes and viral elimination, mediated by dendritic cells and NK. Adaptive immunity also is known as acquired or specific immunity consists of a microbial mediated mechanism and is capable of identifying microbial and non-microbial molecules precisely called antigens."

The adaptive immune system such as lymphocytes comprising antibodies and cytokines and their constituents. The lymphocyte receptors in the innate immune system are far more complex and may identify

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large numbers of foreign substances. There are two forms of adaptive immunity: humoral immunity, mediated by B lymphocytes and secreted antibodies that defend against extracellular microbes and their toxins; and cellular or bacterial immunity, mediated by T lymphocytes that primarily defend against intracellular microbes. The two types of immunity obtained are related by a broad family of proteins known as cytokines, which play an important role in the activation, control, and communication of immune cells.[1]

For the study of the effects of anesthetic drugs on the immune system, various for vitro studies with human immune cells,[10] or animal models were used. Such studies have shown a range of effects, such as improvements in the number and role of immune cells, and effects on patterns of varying immune mediator secretions, Impact of the inflammatory response by releasing cytokines during the postoperative period.[2] Such results can be clinically important as the balance between cytokine secretions pro and anti-inflammation also tissue injury. Several studies have shown the effect of anesthetics on immune responses even in few days after administration.[12,13,14]

Impaired immunity in vivo is frequently found following major surgery and is multifactorial. Procopio et.al performed a randomized clinical trial to assess the independent impact on human immune function between general anesthesia (GA) and lumbar epidural anesthesia (LEA) in the absence of surgical trauma. To the pulmonary clinician, this heralds the dawn of innovative treatments in different fields such as diseases, allergies, and cancer.[3] The immune system mediates many adverse drug reactions. It may be because the drug's therapeutic role affects the immune system.[4] Mechanical ventilation can lead to ventilator-induced lung injury in animals and can contribute to acute lung injury or acute respiratory distress syndrome in humans, both high-strength mechanical ventilation and hyperoxia.[5] In the anesthesia community, the immunopathological effects of prolonged exposure to inhalation anesthesia have reduced neutrophils, leukocytes, B lymphocyte cells and natural killer cells (NK), which are the main features of the immune system.[6] A recent research examining the effects of immunity from first-inhalation anesthesia, halothane, showed that CD4, CD8 cells and B lymphocytes significantly decreased with repeated doses of halothane.[7]

Sevoflurane is a modern form of inhalation anesthesia widely used in the practice of anesthesia today.[8] Sevoflurane is a highly fluorinated methyl-isopropyl ether typically used in the induction and maintenance of general anesthetics. In addition to the anesthetic function it was also proven to be involved in the protective cycle under hypoxia or endotoxemia conditions, often studied in neurons and myocardial tissue.[9] Research conducted by Kidani et al. examined the effect of sevoflurane pretreatment on mortality and inflammation during endotoxin-induced mice shock. Researchers reported that this pretreatment significantly increased the blood pressure, acid-base balance, and decreased the mortality and plasma rates of TNF-α and IL-6, suggesting a weakening of the inflammatory response. [10]

Sevoflurane induces postconditioning symptoms following exposure to hypoxia, or lipopolysaccharides (LPS). In this regard, the postconditioning of sevoflurane has been shown to reduce oxidative blood and brain damage and increase the immunity index in mice with ischemic reperfusion of the brain.[11] Importantly, data from Yue et al. evaluating sevoflurane postconditioning in an acute lung injury model in vitro showed that inflammatory mediators, chemotaxis and neutrophil adherence were significantly reduced.[12]

IL-12 is also known as a stimulant factor for T-cells, since it contributes to the differentiation of CD4 T cells into TH1 cells. IL-12 family cytokines had important therapeutic targets or agents in a number of inflammatory diseases and induced surgical stress.[13] Surgical stress activates the aid's dominant T-cell type 2 (Th2) status and disturbs the cytokine balance between Th1 and Th2. Anesthesia can suppress the stress response to surgery, so it can reduce the imbalance in the Th1/Th2 ratio.[14] In this study, the researcher will investigate the immune system effects of sevoflurane by measuring IFN-π and IL-12.

A craniotomy is a skull opening procedure (cranium) with the purpose of detecting and restoring damage to the brain. The aim of the surgery is to open the skull so it can locate and restore brain damage. Intracranial procedure or also called craniotomy is an intracranial problem-related intervention. How do the effects of sevoflurane and propofol on IFN-γ and IL-12 study on patients with craniotomy surgery ?

II. HYPOTHESIS

1. There are differences of IFN-γ and IL-12 level after anaesthesia using sevoflurane compared the level before anesthesia
2. There are differences of IFN-γ and IL-12 after anaesthesia using propofol compared to the level before anesthesia

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3. There is differences of increase in IFN-γ and IL-12 level after anesthesia with sevoflurane compared to with propofol.

III. METHODS

The population of this study is patients aged between 30-55 years old undergoing craniotomy surgery at Dr. Kariadi hospital. Subjects are patients aged 30-55 years old who undergo craniotomy surgery for tumor removal at Dr. Kariadi Hospital who fulfill the inclusion and exclusion criteria as follows: The total number of subjects in each group is minimum 14 for every group. IN this research will be used 16 patients for every group.

Differences in the means before and after the same anesthesia agent will be analyzed with paired T-test if the data distribution is normal, or with the Wilcoxon rank sum test if the data distribution is not normal. The difference in the means between the two different anesthesia agents will be analyzed using an independent T-test if the data distribution is normal, or with the Mann-Whitney test if the data distribution is not normal.

IV. RESULTS AND DISCUSSION

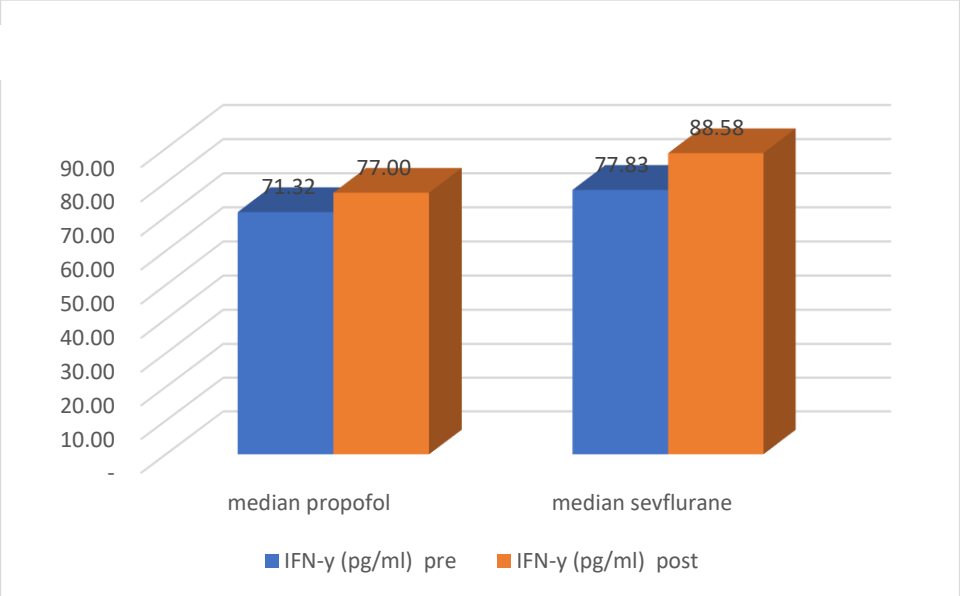
Characteristics of the Subjects

Table 1. Demographic Data

No	Descriptive	Propofol Group n (%)	Sevoflurane Group n (%)	p
1	Sex - Male - Female	 6 (37.5) 10 (62.5)	 3 (18.7) 13 (81.3)	0.217
2	Age,average (SD)	± 45 (5.3) years	± 44.4 (5.8) years	0.7
3	ASA - I - II	 12 (75) 4 (25)	 11 (68.7) 5 (32.3)	0.361
4	Kind of surgery	Intracerebral tumor	Intracerebral tumor	Not tested

The p-value showed that there were no differences between males and females for both groups and also the ASA. The type and duration of surgery were comparable among both groups. Age of the patients between propofol and sevoflurance group was similar and not different significantly.

The Effects of Sevoflurane and Propofol on IFN-γ and IL-12 Levels



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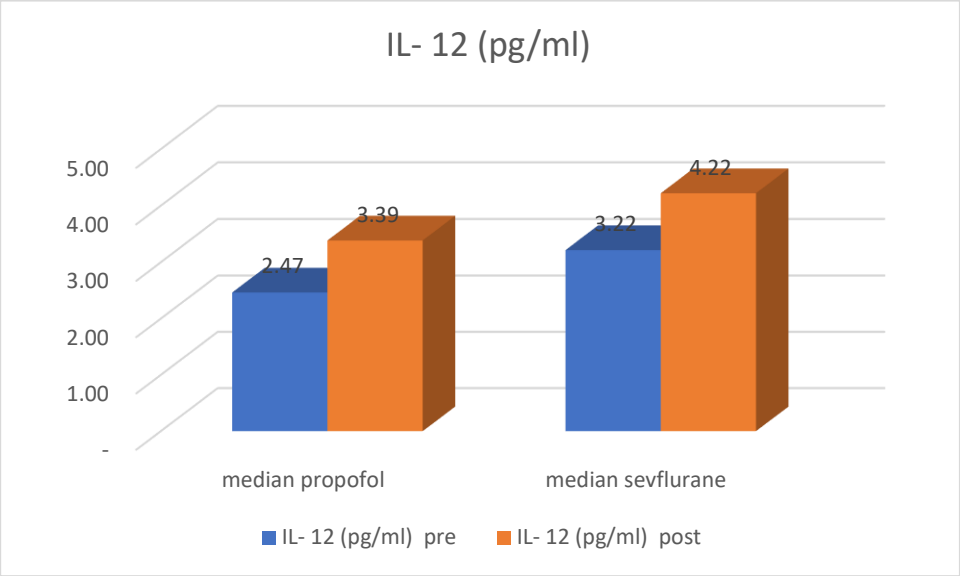

Graph 4.2. plasma IL-12 concentration (pg/ml)

The table 2 showed the level of IFN-γ and IL-12 in sevoflurane group.

Table 2. Level of IFN-γ and IL-12 in Sevoflurane Group

Anestetic agent	**IFN-γ level Median(IQR) (pg/ml)**	**IL-12 level Median(IQR) (pg/ml)**
Before anesthesia with Sevoflurane	71.3 (66.3-81.8)	2.3 (2.1-3.7)
After anesthesia with sevoflurane	77.0 (72.7-90.4)	3.4 (2.9-4.3)
Differences	2.3 (-5.1-18.0)	0.6 (-01-1.0)
p*	0.211	0.049

* Wilcoxon rank sum test

Table 2. showed that the level of IFN-γ increased after anesthesia in sevoflurane group; however the difference was not statistically significant. therefore hypothesis number 1 for IFN-γ is rejected. Table 4.2. also showed that the level of IL-12 significantly increased after anaesthesia using sevoflurane ($p = 0.049$). Therefeore, the hypothesis number 1 for IL-12 is accepted.

Table 3. Level of IFN-γ and IL-12 in Propofol Group

Anestetic agent	**IFN-γ level Median(IQR) (pg/ml)**	**IL-12 level Median(IQR) (pg/ml)**
Before anesthesia with propofol	77.8 (73.1 - 112.2)	3.2 (1.5 - 16.4)
After anesthesia with propofol	88.6 (80.6 - 121.9)	4.2 (3.1 - 11.6)
Differences	7.4 (1.5 – 16.4)	0.8 (0.2 – 1.6)
p*	0.006	0.007

* Wilcoxon rank sum test

Table 3. also showed that the level of IFN-γ and IL-12 significantly increased after anesthesia using propofol. Therefore, the hypothesis number 2 is accepted for both IFN-γ and IL-12.

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Table 4. Difference in Level IFN-γ and IL-12 between Groups

Variables	Groups		p*
	Sevoflurane Median(IQR)	Propofol Median (IQR)	
IFN-γ (pg/ml)	2.3 (-5.1 – 18.0)	7.3 (1.5 – 16.4)	0.006
IL-12 (pg/ml)	0.6 (-0.1 -1.0)	0.8 (0.3-1.6)	0.001

* Wilcoxon rank sum test

Table 4. showed that the level of both IFN-γ and IL-12 were significantly higher in propofol group rather than in sevoflurane group; Therefore, the hypothesis number 3 is accepted for both IFN-γ and IL-12.

Discussion

In this study, the effects of general anesthesia on pro-inflammatory cytokines INF-γ and IL12 were assessed in pre-and post-anesthesia on patients with craniotomy surgery. This study result showed that the level of both IFN-γ and IL-12 were significantly higher in the propofol group rather than in the sevoflurane group. IFN-γ is known as a pro-inflammatory cytokine that plays a central role in infections and autoimmune diseases. It is synthesized by human macrophages in a single cell of human macrophages, in addition to lymphocytes that contribute to the IFN-γ response, and provide another correlation between the innate and acquired immune response. Interferon is also available as a drug. Interferon in the form of drugs works by increasing the body's immune response and inhibiting the growth of viruses, bacteria, or cancer, and also have a role in the immune system.

IL-12 and interferon-gamma, actually represent the inflammation conditions, not directly the immune condition, but they can be considered to represent immune condition because IL-12 and interferon-gamma are pro-inflammation. Inflammation is a response to various kinds of trauma. This matter is the most important part of innate immunity, too is an initiator and also a regulator important in adaptive immune responses. Inflammation involves tissue micro vascularization affected, especially the postcapillary venules. System Immune patients undergoing surgery influenced by anesthetic actions as well as the act of surgery itself. Hypothalamic-pituitary-adrenal axis the sympathetic nervous system will be active along with stress surgery, blood transfusion, hypothermia, hyperglycemia, and pain. Anesthetic action causing direct emphasis on activity cellular and neuro-hormonal immune system so that it influences cell function immunocompetent and expression and secretion inflammatory mediator. Immunosuppression by anesthesia especially occurs in patients of intracerebral tumors, such as natural killer (NK) dysfunction and lymphocytes which accelerate growth and metastasis of malignant cells so it will worsen the prognosis. Leukocytes are part of innate immunity. The cellular component of immunity innate consists of several types of cells and many found at the entry point of the pathogen. Examples of these cells are natural killer cells (NK), polymorphonuclear cells (PMN), macrophages, and dendritic cells Neutrophil/lymphocyte ratio (NLR) is a simple marker of the inflammatory response. NLR value peripheral blood is used as a parameter that provides information on the relationship between the inflammatory environment and stress physiology. Postoperative Value of NLR in surgery patients undergoing spinal anesthesia lower compared to patients who undergo general anesthesia. If IL12 level increase, mean inflammation increase, this is mean that immune become increase (good condition). It has been shown that IL-12 cytokine has an effect on both immune and hematological functions. It has been shown to be necessary for the independent induction of IFN-γ T cells. Therefore, IL-12 thus function to stimulates and binds innate and acquired immune responses. When the patients undergo the surgery, therefore the surgical trauma and anesthesia influence the immunological and inflammatory responses. Anesthetic agents like sevoflurane and propofol modulate the inflammatory reactions in this sense. The stress of surgery will result in an increase of level IFN-γ and IL-12 as a response to the inflammatory reaction.

After surgery and give anesthesia, the result showed that the level of IFN-γ increased after anesthesia with sevoflurane; however, the difference was not statistically significant. therefore hypothesis number 1 is rejected. Meanwhile, the level of IL-12 increased after anesthesia using sevoflurane; however, the increase was significant. Therefeore, hypothesis number 1 is accepted. This is because the patients' age also gives an effect on the increase of level IFN-γ and IL-12. Sevoflurane not

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give too significant effect to the patients between before and after surgery and given anesthesia. This indicates that sevoflurane can reduce patients' stress and good pro-inflammatory.

Another result of this study showed that the level of IFN-γ increased after anesthesia with propofol; however the difference was statistically significant, therefore hypothesis number 2 is accepted. The level of IL-12 increased after anesthesia using propofol, however, the increase was significant. Therefeore, the hypothesis number 2 is accepted. Thus the hypothesis 3 accepted because there are differences effect between propofol and sevoflurane as anesthesia agents. There are different effects of sevoflurane and propofol on pro-inflammatory cytokines. This research also supported by previous research done by Dang et al. (2018) that concluded general anesthesia combined with regional anesthesia is better than single-use general anesthesia. Most inhaled anesthetics, opioids, local anesthetics, and other intravenous anesthetics can reduce immunity to a certain extent, which sometimes leads to an increased recurrence of malignant tumors. However, tramadol, selective nonsteroidal anti-inflammatory analgesics, and propofol have protective effects on the immune function of the body and can reduce the recurrence and metastasis of the tumor. Therefore, it is important to make a careful anesthesia plan and to select appropriate narcotic drugs for patients with malignant tumors, since these decisions will have a crucial impact on the therapeutic effect and prognosis.

Also supported the result of a previous study done by Ji et al. (2011) that stated immune response in the process of tumor development is not just a single factor, but it plays a multifaceted role affecting tumor initiation, growth, progression, and other processes. The immune system regulates and promotes cancer programs, a process known as immunoediting. There are three phases to this process: elimination, balance, and escape. Although experimental evidence shows that inflammation can also promote the occurrence and development of tumors, the immune inflammatory response in colon carcinogenesis requires further study and is still under debate. Some clinical data show that the immune response inhibits the tumor. However, other investigators have concluded that the opposite is true. IL-12 is an early promoter of T-cell-induced inflammatory responses and can amplify the inflammatory response by promoting the release of proinflammatory cytokines. Intravenous anesthesia can maintain a safe, constant concentration of drug treatment during surgery and can reduce the stimulation of surgical trauma. Intravenous anesthesia can also reduce the intraoperative inflammatory response albeit affecting the patient's immune system function. Immune system disorders or inhibition during the perioperative period can cause postoperative complications, especially in cancer patients. Immunosuppression after surgery can accelerate the spread of residual cancer cells and promote a new transfer.

In this study, the patient characteristics, preoperative values in the laboratory, and surgical data were comparable in craniotomy surgery between two groups and ASA I /II. The advantage of this study is to test the different effects between anesthetic agents of propofol and sevoflurane. thus it shows that propofol increases the pro-inflammatory cytokines significantly, while sevoflurane does not significantly increase these cytokines. The weakness of this study is the limited samples and not include the BIS (Bispectral Index), as confounding variables. The BIS is derived from a non-invasive technology, which provides a composite value of cortical activity between 0 (no cortical activity) and 100 (completely wake) represents a general anesthesia condition. A longer observation period would still be necessary to clarify the possible effects of anesthetics on pro-inflammation cytokines after tumor craniotomy.

The implication of this study was that propofol increases the level of IFN-γ and IL-12, therefore in the anaesthesiologists and surgeons must be more careful during the post-operation, particularly on the manifestations of an inflammatory reaction, such as fever, hemodynamic and respiratory instability. Our findings should incite future studies to prove a potential medically important anesthesia agent's role with pro-inflammatory other cytokines.

V. CONCLUSION

According to the analysis data, the conclusion in this reserach as follows:

1. When sevoflurane was used as an anesthesia agent, the level of IFN-γ dose not significantly increase while the level of IL-12 significantly increases.
2. When propofol was used as an anesthesia agent, the level of both IFN-γ and IL-12 increase significantly.
3. The increase of both IFN-γ and IL-12 level after anesthesia with propofol is significantly higher than those with sevoflurane.

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4. Propofol exerts a bigger pro-inflammatory response then sevoflurane in patients undergo craniotomy surgery.

Recommendation for the future research based on this research result as follows:

1. BIS (Bispectral Index) can be considering as confounding variables, also a longer observation period would still be necessary to clarify the possible effects of anaesthetics on pro-inflammation cytokines after tumor craniotomy.
2. Future studies to prove other anesthesia agents' role on pro-inflammatory other variables would still be important to do.
3. Adding more components of the immune system in future studies or analyzes, and evaluating exposure to anesthesia after more than two hours.

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